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Baron & Warren 18 South End Kensington
London W8 5BU(GB)(54) **Pharmaceutical composition in sustained release unit dose form and process for its preparation.**

(57) A pharmaceutical composition of a medicament, such as a 5-(pyridinyl)-2(1H) pyridone, in sustained release unit dosage form for oral administration. The composition is in the form of beads within a capsule of gelatin or the like. Each bead comprises an inert particulate core having adhered thereto a coating of particles of the medicament. This coating is in turn surrounded by a sustaining coating of three different polymers with different solubility profiles to allow a sustained release of the medicament both in the low pH environment of the stomach and at a higher pH values prevailing in the intestine.

"PHARMACEUTICAL COMPOSITION IN SUSTAINED RELEASE
UNIT DOSE FORM AND PROCESS FOR ITS PREPARATION"

1 This invention relates to a sustained release
form of a medicament for administration by the oral
route.

 The use of enteric coatings on medicaments in
5 order that the medicaments shall pass through a patient's
stomach unchanged and thus ensure that the active
ingredient or ingredients are released in the patient's
small intestine where the pH is normally between
5.5 and 7.5 is now an established method of treatment.
10 This prevents irritation of the gastrointestinal
tract and is often convenient as it may make it
unnecessary for a patient to take a dose of medicament
more often than two or three times a day to maintain
effective blood levels of medicament. A substantial
15 number of synthetic polymeric materials have been
proposed for use in such formulations and the nature
of the coatings used in the formulations have varied
considerably depending upon the results sought.
 Thus the synthetic polymeric materials used have
20 included polymers of vinyl monomers such as vinyl
pyrrolidone and vinyl acetate phthalate and the semi-
synthetic derivatives of celluloses such as cellulose
ethers and carboxycelluloses, e.g. cellulose acetate
25 phthalate and hydroxypropylmethyl cellulose phthalate.

 In some cases partial solution of a medicament
in the patient's stomach is required especially if
gradual solution in both the stomach and the small
intestine is the desirable course to aim at. This
30 presents problems because of the differences in the
pH values prevailing in the stomach and the intestine,
and in the differences in the chemical and physical

1 properties of particular medicaments when submitted
to these differing pH conditions. In general the
differences are most difficult to overcome with medic-
aments containing one or more amino groups in the
5 molecule. Individual solutions have to be found
to the particular problems posed by each system.

In two or three cases in which the medicament
is only soluble at pH values between 1 and 4 solution
can take place naturally in the stomach but does
10 not occur at all in the small intestine. To overcome
this difficulty it has been proposed to include a
readily soluble pharmacologically acceptable acid
in the inner or core portion of each unit of medicament:
the amount of this acid may be two or more molecules
15 for each molecule of medicament and it enables sufficiently
acid conditions to be set up locally in the small
intestine for the medicament to dissolve and be absorbed
through the walls of the intestine. The core is
surrounded by a semipermeable coating containing
20 a mixture of film-forming materials one of which
is soluble and the other of which is insoluble in
the gastric juices (see US-A-4 361 546, 4 367 217
and 4 438 091). It will be appreciated that in this
way a gradual release of medicament can be brought
25 about and consequentially there is gradual absorption
through the walls of the stomach and the small intestine.
However it is limited to the particular solubility
characteristics indicated for the medicament.

A different problem arises when a medicament
30 has a high solubility in the low pH gastric

1 juices and a very much lower solubility in the
higher pH intestinal juices, which lower
solubility may nevertheless
be sufficient for a sustained release formulation.

5 We have now encountered a group of medicaments in
which such solubility characteristics have been found
to exist and for which a sustained release formulation
is required.

10 IN GB-A-2 065 642 there are described a number
of 5-(pyridinyl)-2(1H) pyridones which are reported
to be useful as cardiogenic agents. Certain of these
compounds have been found to show promise for use
in vivo and to be potential materials for use with
human patients but they have one important drawback
15 viz that they are very readily eliminated from the
human system as demonstrated by the plasma profiles
obtained after administration to human patients.
These compounds have been found to have much greater
solubility in the gastric juices at pH 1.5 than they
20 have at pH 4.5. In one instance the solubility is
substantially fifty times greater at pH 1.5 than
it is at pH 5 to 8.

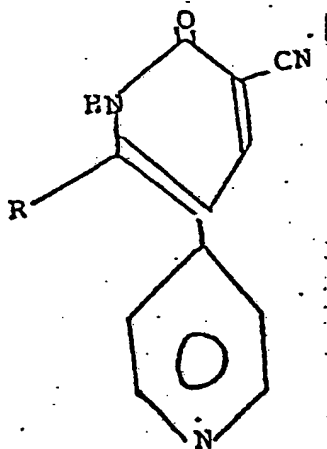
It is accordingly an object of this invention
to provide a sustained release form of the above
25 mentioned medicaments and others that are orally
administered and have a high solubility in gastric
juices but are very readily eliminated from the human
system, which form will overcome this drawback.

Accordingly the invention consists in a pharma-
30 ceutical composition of a medicament in sustained
release unit dosage form for oral administration,
comprising a plurality of beads within a closed container
of a gastric juice-soluble material, characterised
in that each said bead has an inert particulate core

1 having adhered thereto a coating of particles of said
medicament, said coating of medicament being surrounded
by a sustaining coating comprising at least three admixed
5 polymers, a first said polymer being soluble in gastric
juices at all pH values encountered in the gastrointes-
tinal tract, a second said polymer being substantially
insoluble in gastric juices at pH values below 3 but sol-
uble therein at pH values of 5 and above and the third
10 said polymer being insoluble in the contents of the
gastrointestinal tract at all pH values normally
encountered therein, and the three polymers being
present in such proportions as to permit a substant-
ially uniform release of the medicament during passage
of the beads through the stomach and gastrointestinal tract..

15 It is preferred that the weight of the polymer
which is insoluble in the contents of the gastrointestinal
tract is greater than the sum of the weights of the
other two polymers present in the sustaining coating.
A convenient ratio of the weight of the insoluble
20 polymer to the combined weights of the other two
polymers present in the sustaining layer has been
found to be from 3 : 2 to 2 : 1.

The invention has been found to have a particular
application to the formulation in unit dosage form
25 for administration by the oral route of pyridyl-(1H)
pyridones having the general formula



(I)

1 in which R is an alkyl group having 1 to 4 carbon
atoms. With such materials it has been found that
upon administration by the oral route the concen-
tration of the medicament in the plasma rises very
5 rapidly during the first hour and then falls by approx-
imately two-thirds of the maximum reached during the
second hour. Subsequently it falls at a somewhat
diminishing rate during the third and subsequent hours.
If a single dose is to be sufficient to maintain effec-
10 tive blood levels in a patient for a substantial number
of hours e.g. 4 or 8 hours a system needs to be
devised in which only a portion of the dosage is made
available for absorption into the blood at any one time.
Continual release of the medicament will maintain effective
15 blood levels until the next dose of medication is taken. The
rate of dissolution (and therefore availability) has
been found to be determined by the pH of the
particular part of the gastrointestinal tract.

It has been found that in the case of the
20 pyridyl-pyridones the rate of dissolution is greatest
in the range of lowest pH value which is in the
stomach and the rate of dissolution decreases as the pH
rises along the passage of the upper gastrointestinal
tract.

25 Consequently the polymers used and the proportions
of these in the sustaining layer will determine the
release characteristics of the medicament from the
dosage form.

We prefer to use nonpareils as the inert substrate
30 material of the beads that we prepare.

The substrate is then coated with particles

1 of the medicament in solid form. It may be necessary
to convert a medicament to a derivative such as a
salt in order to obtain it in solid form. Medicaments
available in solid form may need to be ground in
5 order to obtain particles sufficiently small to be
conveniently adhered to the particles of core material.
The latter are conveniently of a size which will
pass a 25 US standard mesh and be retained on a 30 US
standard mesh. To adhere the particles of solid
10 medicament to the inert substrate we prefer to use
a water soluble pharmacologically acceptable adhesive
such as a suitable grade of hydroxypropylmethylcellulose.
The hydroxypropylmethylcellulose used may be that known
as "Pharmacoat 606", a 6-centipoise grade of hydroxy-
15 propylmethylcellulose. A thorough dispersion of the
solid medicament in Pharmacoat 606 solution is then
prepared and used to coat the nonpareils or other
particulate inert substrate material in a coating
column and dry the coated material at a raised temp-
20 erature, e.g. 60°C.

The sustaining coating essentially contains
three polymers each of which behaves differently in
the gastrointestinal tract. All three polymers may
be cellulose derivatives and each of the polymers
25 may be a mixture. However, whether each be a single
individual or a mixture it must conform to certain
solubility requirements in relation to the gastro-
intestinal tract.

The first polymer should be soluble in the gastric
30 juices at all pH values encountered in the stomach and
the intestine. In the case of the pyridyl pyridones
this includes the pH range over which these substances
exhibit their maximum solubility in the gastric juices:

- 1 when this is the case the preferred polymer is hydroxy-
propylmethylcellulose. Other polymers which may be
used for this purpose include polyvinylpyrrolidone
and sodium carboxymethylcellulose. When it is
5 essential to reduce the rate of dissolution of the
medicament at pH values of the order of 1.5 the
proportion of this polymer in the mixture of polymers
should be kept low e.g. 15% - 20% or less by weight
of the whole mixture of polymers.
- 10 The second polymer used is one which is sub-
stantially insoluble in gastric juices at pH values
below 3 but soluble therein at pH values of 5 and
above. The use of such a polymer ensures that while
this part of the coating remains substantially intact
15 at the pH values normally encountered in the stomach,
typically 1.5 - 2.0, at pH 5 and above the permeab-
ility of the coating to the medicament increases
and this rise in permeability counteracts the
reduced solubility of the medicament to reduce the pH
20 dependence of the release rate. This polymer may
start to become soluble at pH values lower than 5,
for example at 3.5 or 4. The preferred polymer for
this purpose is hydroxypropylmethylcellulose phthalate.
Other polymers which are suitable for this purpose
25 include copolymers of the lower alkyl methacrylates
and polyvinylacetate phthalate.

The third polymer used should be one which is
insoluble at all pH values normally encountered in
the gastrointestinal tract. In the lower gastro-
30 intestinal tract pH values of about 7.5 are normally
to be expected and this is the minimum value for

1 insolubility of the third polymer. The preferred
third polymer is ethyl cellulose. Other polymers
which may be used include copolymers of the lower
alkyl methacrylates in which the copolymerising monomer
5 contains a hydrophilic group.

Other factors which affect the rate of release
of the medicament present include the thickness of
the sustaining coating and the ratios of the three
polymers present in the sustaining coating. Regarding
10 thickness of the coating the thicker the coating
the slower the rate of release at all pH values.

The polymer ratios have an important bearing
upon the rate of release of medicament at all pH
values. Increase in the ratio of the first polymer
15 to the third polymer raises the rate of release of
medicament at low pH values, i.e, in the stomach
whilst decrease in this ratio reduces the rate of
release. Increase in the ratio of the second polymer
to the third polymer increases the rate of release
20 at pH values above about 5. Increase in the ratio
of the second polymer to the first polymer without
changing the proportion of the third polymer increases
the rate of release at pH values above about 5 and
decreases the rate of release at pH values below
25 about 5.

According to a further aspect of the invention
there is provided a process for producing a pharmaceutical
composition as defined above wherein the beads are prepared
by coating inert core particles with particles of the medic-
30 ament and a binder for adhering said medicament particles
to said core particles, and applying to said coated core
particles a sustaining coating solution comprising at least
the three polymers of differential solubility defined above.

In producing the unit dosage form of the product in accordance
35 with the invention one may, for example, add 18 parts by weight
of the three selected polymers to 261 parts by weight of a dispersion
medium therefor. When the three polymers are cellulose ethers and ether

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1 esters, ethanol is a suitable medium. The resulting
mixture is stirred until well dispersed and a low
boiling solvent (e.g. methylene chloride) is then
added and stirring continued until a clear solution
5 is obtained. Nonpareils coated with medicaments
are placed in a coating column or pan and the solution of the three polymers is then gradually fed into
the column or pan whilst passing a current of warm
air through the nonpareils until dry coated non-
10 pareils are obtained.

The dried coated nonpareils are then weighed
into unit dosage quantities and separate weighed
quantities are fed into hard gelatine capsules and
each capsule closed.

15 The following examples illustrate the invention.
All parts are by weight.

PREPARATION 'A'

Production of Nonpareils coated with medicament

11 parts hydroxypropylmethylcellulose (Pharmacoat
20 606) are suspended in 111 parts of purified water
previously heated to boiling. 440 additional parts
of water are then added to the suspension and the
whole stirred until a diluted Pharmacoat suspension
has formed.

25 11 parts of 1,2-dihydro-6-methyl-2-oxo-5-
(4-pyridinyl) -nicotinyl nitrile are stirred into
the Pharmacoat suspension until well dispersed. 200
parts of nonpareils (sucrose base passing a 25 US
standard mesh and being retained on a 30 US standard
30 mesh) are placed in a coating column or pan and
whilst passing an atomizing current of warm air

- 1 therethrough gradually feed in the diluted Pharmaccoat
suspension. After all the Pharmaccoat suspension has
been added continue the passage of the current of
warm air until the coated nonpareils are dry.

5 EXAMPLE 1

There are placed in a suitable container 261
parts of ethanol, 11.70 parts of ethyl cellulose,
3.60 parts of hydroxypropylmethylcellulose and 2.70
parts of hydroxypropylmethylcellulose phthalate.

- 10 The solids are stirred in until well dispersed and
there is then added to the dispersion 621 parts of
methylene chloride. A clear solution should result.

- Into a coating column or pan there are placed 222
parts of coated nonpareils prepared as described
15 under Preparation A. Whilst passing an atomising
current of warm air through the column the clear
solution above described is gradually fed into the
coating column or pan. After all the solution has
been introduced into the column or pan passage of
20 warm air is continued until the nonpareils are dry.

- The product consisting of nonpareils first
coated with medicament and then coated with sustaining
coating of three polymers is then removed from the
column and after cooling to room temperature, weighed
25 out into portions each containing the required
quantity of medicament which are separately fed
into standard hard gelatin capsules and closed.

EXAMPLE 2

- 272.72 parts of nonpareils (passing a 25 US
30 standard mesh and being retained on a 30 US standard
mesh) were coated with a dispersion prepared from

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- 1 15.0 parts of the same nitrile and 15.0 parts of
hydroxypropylmethylcellulose (6 centipoises) as
described in Preparation A.

A sustaining coating solution is prepared from
5 6 parts of ethylcellulose, 2 parts of hydroxypropyl-
methylcellulose (6 centipoises) and 2 parts of hydroxy-
propylmethylcellulose phthalate and used to coat
the already coated nonpareils as described in Example 1.
The subsequent procedure is also as described in
10 Example 1.

EXAMPLE 3

Nonpareils are coated with nitrile as described
in Example 2. A sustaining coating solution is then
prepared from 12.42 parts of ethylcellulose, 4.14 parts
15 of hydroxypropylmethylcellulose (6 centipoises) and
4.14 parts of hydroxypropylmethylcellulose phthalate
and the subsequent procedure is then as described
in Example 1.

EXAMPLE 4

20 Nonpareils are coated with nitrile as described
in Example 2. A sustaining coating solution is then
prepared from 15.95 parts of ethylcellulose, 4.91
parts of hydroxypropylmethylcellulose and 3.68 parts
of hydroxypropylmethylcellulose phthalate and the
25 subsequent procedure is then as described in Example 1.

EXAMPLE 5

114 parts of nonpareils (passing a 25 US standard
mesh and being retained on a 30 US standard mesh) were
coated with a dispersion prepared from 15 parts of the
30 same nitrile and 6.0 parts of hydroxypropylmethyl-
cellulose (6 centipoises) as described in

- 1 Preparation A. A sustaining coating solution is
prepared from 5.63 parts of ethylcellulose, 1.88
parts of hydroxypropylmethylcellulose (6 centipoises)
and 1.88 parts of hydroxypropylmethylcellulose phthalate
5 and used to coat the already coated nonpareils as
described in Example 1. The subsequent procedure
is also as described in Example 1.

EXAMPLE 6

- Nonpareils are coated with nitrile as described
10 in Example 5. A sustaining coating solution is then
prepared from 6.0 parts of ethylcellulose, 1.90 parts
of hydroxypropylmethylcellulose (6 centipoises) and
2.10 parts of hydroxypropylmethylcellulose phthalate.
The subsequent procedure is then as described in
15 Example 1.

- Other nitriles having the general formula I
have been prepared in sustained form by proceeding
in the same manner as that illustrated in the above
examples and the method is applicable to other solid
20 medicaments having an elimination half-life of the
order of 0.5 to 4 hours that can be applied to a core
such as a nonpareil. In addition to cores formed
of one or more normally crystalline sugars, with or
without cellulose, inorganic materials such as calcium
25 phosphate may be used as the core material.

- The availability of sustained release formulations
in accordance with this invention is of great assistance
to the patient since it means that a patient does
not need a unit dosage as frequently as would otherwise
30 be the case to maintain effective blood levels of

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1 medicament. This minimises the risk of omission to
 take a dose at the correct time as well as avoiding
 the need to take a dose during the night.

The action of the controlled in vivo release
 5 resulting from the use of the formulations in acc-
 ordance with the invention results in controlled and
 reproducible therapy by avoiding peak and trough
 periods in the plasma levels of patients taking the
 prescribed medicament. Such peaks and troughs are
 10 otherwise readily observable with a medicament having
 as short an elimination half-life period as 1 or 3
 hours. A continuous release of medicament during
 passage through the stomach and the gastrointestinal
 tract is secured by the use of three polymers as
 15 described and this is effected in a simple coating
 operation.

The products of the present invention have been
 compared with conventional caplets containing an
 equal total weight of 1.12-dihydro-6-methyl-2-oxo-
 20 5-(4 pyridinyl-nicotinylitrile) (Compound A) in order
 to determine the bioavailability of the compound when
 administered to a patient in those forms. The products
 of the present invention were made up using nonpareils
 as the core material so that each capsule contained

25	Compound A	15. 0 mg
	Pharmacoat 606	6. 0 mg
	Nonpareils (25-30 mesh)	114. 0 mg
	Ethyl cellulose	6. 00 mg
	Pharmacoat 606	1. 90 mg
30	HP-50 (hydroxypropylmethyl cellulose)	2. 10 mg

- 1 The total weight of the filling for each capsule shell was 145.0 mg and this contained 15.0 mg of Compound A.

5 The conventionally formulated caplets respectively contained 5 mg and 10 mg of Compound A, one of each being administered to provide the reference quantity of Compound A. The compositions of the two caplets were as follows:

Core:

10	Compound A	10 mg	5 mg
	Lactose Excipient	209 mg	104.5 mg
	Pre-gelatinized starch	80 mg	40 mg
15	Microcrystalline cellulose AVICEL	100 mg	50 mg
	Magnesium stearate	<u>1 mg</u>	<u>0.5 mg</u>
	Core total:	400 mg	200 mg

Coating:

20	Hydroxypropyl-methylcellulose	8.33 mg	3.7 mg
	Glyceryl triacetate	1.67 mg	0.739 mg
	Titanium Dioxide	0.265 mg	1.480 mg
	Quinolone Yellow Lake	0.175 mg	0.0704 mg
25	Erythrosine Lake	0.060 mg	
	Indigo Carmine Lake		<u>0.0131 mg</u>
	Total	410.5 mg	206.0 mg

- 30 The conventional caplets and capsules were given to a number of volunteers and the concentrations of Compound A in the plasma of the volunteers at various time intervals from 0.17 to 24 hours from the time of administration were determined. Graphs were prepared

- 1 from the results obtained. An interval of one week
was allowed between the first and second treatments
for each volunteer.

Samples of plasma were taken from each volunteer
5 at 10, 20, 30 and 45 minutes during the first hour
after administration, then at half hourly intervals
for 1 to 4 hours and then at 5, 6, 8, 11, 14 and 24
hours after administration. Parameters determined
included maximum drug concentration in the plasma
10 (C_{max}), time to reach maximum concentration (t_{max}).
From the graphs drawn up the area under the curves
of plasma concentration against time up to the last
point of sampling was calculated using the trapezoidal
rule (AUC). The graphs provided plasma profiles
15 for the several test formulations from which the
following mean data were read:

	<u>C_{max}</u> <u>ng/ml</u>	<u>T_{max}</u> <u>Time (hrs)</u>
Conventional caplets	422	0.67
Capsules	138	2.95

- 20 The plasma profiles with capsules were much flatter
and broader than those obtained with caplets.

The mean relative bioavailability was 92%.
This figure is based upon the areas AUC under the
graph determined as outlined above.

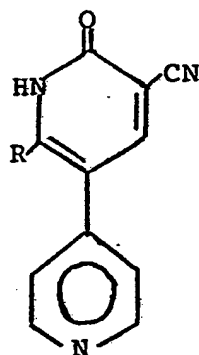
- 25 The number of volunteers for whom the bio-
availability was at least 75% of that obtained from
caplets was 10 out of 10 in the case of capsules.
The 75% figure is regarded as a criterion for a
satisfactory sustained release formulation and it
30 is apparent that this is consistently obtained in

1 the case of the capsules. No adverse reactions were
reported by volunteers to whom a capsule had been given.
It thus becomes apparent that capsules are a very
satisfactory way of formulating materials having
5 high solubility in gastric juices and lower, but
nevertheless appreciable, solubility in the juices
present in the small intestine to obtain a sustained
release form.

CLAIMS

- 1 1. A pharmaceutical composition of a medicament in
sustained release unit dosage form for oral adminis-
tration, comprising a plurality of beads within a
closed container of a gastric juice-soluble material,
5 characterized in that each said bead has an inert
particulate core having adhered thereto a coating
of particles of said medicament, said coating of
medicament being surrounded by a sustaining coating
comprising at least three admixed polymers, a first
10 said polymer being soluble in gastric juices at all
pH values encountered in the gastrointestinal tract,
a second said polymer being substantially insoluble
in gastric juices at pH values below 3 but soluble
therein at pH values of 5 and above and the third
15 said polymer being insoluble in the contents of
the gastrointestinal tract at all pH values normally
encountered therein, and the three polymers being
present in such proportions as to permit a substantially
uniform release of the medicament during passage
20 of the beads through the stomach and gastrointestinal
tract.
2. A pharmaceutical composition according to claim
1, characterized in that the weight of the insoluble
third polymer in the sustaining coating is greater
25 than the sum of the weights of the other two said
polymers.
3. A pharmaceutical composition according to claim
2, characterized in that the ratio of the weight
of the third polymer to the sum of the weights of
30 the other two polymers is from 3:2 to 2:1.

4. A pharmaceutical composition according to any preceding claim, characterized in that said first polymer constitutes 20 wt.% or less of the polymer mixture forming the sustaining coating.
5. A pharmaceutical composition according to any preceding claim, characterized in that the medicament is a pyridyl-(1H)-pyridone having the general formula:



(I)

- wherein R is an alkyl group having 1 to 4 carbon atoms, or a solid derivative thereof.
6. A pharmaceutical composition according to any preceding claim, characterized in that the inert cores of the beads are in the form of nonpareils.
7. A pharmaceutical composition according to any preceding claim, characterized in that said first polymer is selected from hydroxypropylmethylcellulose and polyvinylpyrrolidone.
8. A pharmaceutical composition according to any preceding claim, characterized in that said second polymer is hydroxypropylmethylcellulose phthalate.
9. A pharmaceutical composition according to any preceding claim, characterized in that said third polymer is ethyl cellulose.

- 1 10. A process for producing a pharmaceutical
composition of a medicament in sustained release
unit dosage form for oral administration, comprising
a plurality of beads within a closed container of
5 a gastric juice-soluble material, characterized in
that said beads are prepared by:

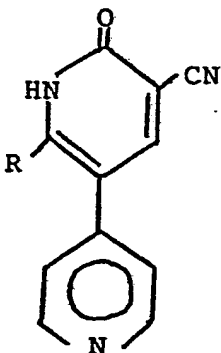
coating inert core particles with particles
of said medicament and a binder for adhering said
medicament particles to said core particles and

- 10 applying to said coated core particles a
sustaining coating solution comprising at least three
admixed polymers, a first said polymer being soluble
in gastric juices at all pH values encountered in the
gastrointestinal tract, a second said polymer being
15 substantially insoluble in gastric juices at pH
values below 3 but soluble therein at pH values of
5 and above and the third said polymer being insoluble
in the contents of the gastrointestinal tract at all
pH values normally encountered therein, and the three
20 polymers being present in such proportions as to
permit a substantially uniform release of the medic-
ament during passage of the beads through the stomach
and gastrointestinal tract.

11. A process according to claim 10, characterized
25 in that said sustaining coating is formed by applying
to the medicament-coated core particles a solution
of said three polymers in a volatile solvent therefor
and evaporating the solvent from the particles thus
coated.

- 30 12. A process according to claim 11, characterized
in that said solution is produced by forming a disper-
sion of the three polymers in a suitable medium,
adding a low boiling solvent to the dispersion and
stirring to give a clear solution.

13. A process according to claim 11 or claim 12, characterized in that the sustaining coating is applied by placing the medicament-coated core particles in a coating column or pan and feeding the polymer solution into the column or pan while passing a current of air through the particles to produce dry coated beads.
14. A process according to any one of claims 10 to 13, characterized in that the medicament is a pyridyl-(1H)-pyridone having the general formula:



(I)

wherein R is an alkyl group having 1 to 4 carbon atoms, or a solid derivative thereof.

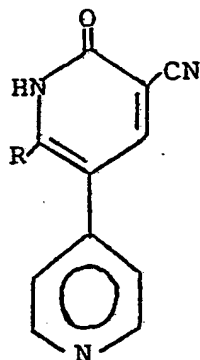
CLAIMS

- 1 1. A process for producing a pharmaceutical comp-
osition of a medicament in sustained release unit dosage
form for oral administration, comprising a plurality
of beads within a closed container of a gastric
5 juice-soluble material, characterised in that said
beads are prepared by:
- coating inert core particles with particles
of said medicament and a binder for adhering said
medicament particles to said core particles and
10 applying to said coated core particles a
sustaining coating solution comprising at least three
admixed polymers, a first said polymer being soluble
in gastric juices at all pH values encountered in
the gastrointestinal tract, a second said polymer
15 being substantially insoluble in gastric juices at
pH values below 3 but soluble therein at pH values
of 5 and above and the third said polymer being
insoluble in the contents of the gastrointestinal
tract at all pH values normally encountered therein,
20 and the three polymers being present in such prop-
ortions as to permit a substantially uniform release
of the medicament during passage of the beads through
the stomach and gastrointestinal tract.
2. A process according to claim 1, characterised
25 in that said sustaining coating is formed by applying
to the medicament-coated core particles a solution
of said three polymers in a volatile solvent therefor
and evaporating the solvent from the particles thus
coated.
- 30 3. A process according to claim 2, characterised
in that said solution is produced by forming a disper-

1 sion of the three polymers in a suitable medium,
adding a low boiling solvent to the dispersion and
stirring to give a clear solution.

4. A process according to claim 2 or claim 3,
5 characterised in that the sustaining coating is applied
by placing the medicament-coated core particles in
a coating column or pan and feeding the polymer solution
into the column or pan while passing a current of
air through the particles to produce dry coated beads.

10 5. A process according to any preceding claim
characterised in that the medicament is a pyridyl-
(1H)-pyridone having the general formula:



(I)

15 wherein R is an alkyl group having 1 to 4 carbon atoms,
or a solid derivative thereof.

20 6. A process according to any
preceding claim characterised in that the weight
of the insoluble third polymer in the sustaining
coating is greater than the sum of the weights of
the other two said polymers.

30 7. A process according to claim 6,

1 characterised in that the ratio of the weight of
the third polymer to the sum of the weights of the
other two polymers is from 3:2 to 2:1.

8. A process according to any
5 preceding claim, characterised in that said first
polymer constitutes 20 wt.% or less of the polymer
mixture forming the sustaining coating.

9. A process according to any
preceding claim, characterised in that the inert
10 core particles are in the form of nonpareils.

10. A process according to any
preceding claim, characterised in that said first
polymer is selected from hydroxypropylmethylcellulose,
sodium carboxymethyl cellulose and polyvinylpyrrolidone.

15 11. A process according to any
preceding claim, characterised in that said second
polymer is hydroxypropylmethylcellulose phthalate.

12. A process according to any
preceding claim, characterised in that said third
20 polymer is ethyl cellulose.